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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/552,082	10/05/2005	Garry Pairaudeau	06275-472US1 101017-1P US	8802
26164 7590 06/09/2008 FISH & RICHARDSON P.C. P.O BOX 1022 MINNEAPOLIS, MN 55440-1022			EXAMINER YOUNG, SHAWQUA	
			ART UNIT 1626	PAPER NUMBER
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/552,082	<b>Applicant(s)</b> PAIRAUDEAU ET AL.	
	<b>Examiner</b> SHAWQUIA YOUNG	<b>Art Unit</b> 1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 29 February 2008.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-4,6-8,10-14 and 16-18 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 1-4,6-8,13,14 and 16-18 is/are allowed.
- 6) ☒ Claim(s) 10-12 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)          | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

### **DETAILED ACTION**

Claims 1-4, 6-8, 10-14, and 16-18 are currently pending in the instant application. Applicants have added claim 18 in an amendment filed on February 29, 2008.

#### **I. *Response to Arguments***

Applicant's amendment, filed February 29, 2008, has overcome the objection of claims 1-4, 6-8, 13-14, 16 and 17 as containing non-elected subject matter and the objection to the title of the invention for not being descriptive. The above objections are withdrawn. The Examiner has rejoined claims 10-12 for examination.

However, upon further examination of the current amendments to the claims, a new ground(s) of rejection is made in view of claims 10-12 under 35 USC 112, first paragraphs as failing to comply with the enablement requirement.

#### **II. *Rejection(s)***

##### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue".

In In re Wands, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

In the instant case,

***The nature of the invention***

The nature of the invention of claim 10 is a method of treating a disease mediated by prostaglandin D<sub>2</sub>, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt as defined in claim 1. Claim 11 is drawn to a method of treating a respiratory disease in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, as defined in claim 1. Support for the intended use of the instant compounds for ligand binding assay at PGD<sub>2</sub> is found on pages 30-31 of the specification.

***The state of the prior art and the predictability or lack thereof in the art***

The state of the prior art is that the pharmacological art involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease by what mechanism). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In *re Fisher*, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is the more specific enablement is necessary in order to satisfy the statute. In the instant

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case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to therapeutic effects of cognitive disorders by inhibiting prostaglandin D2 would make a difference.

Applicants have included "prophylactic" in the definition of "treatment" on page 11 of the specification.

Applicants are claiming a method of treating or preventing a disease mediated by prostaglandin D2. Further, applicants have disclosed a laundry list of diseases or disorders that can be treated by using the claimed invention on pages 11-15.

Some the diseases include:

**(gastrointestinal tract)** Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, irritable bowel disease; food-related allergies which have effects remote from the gut, (such as migraine, rhinitis and eczema);

**(central and peripheral nervous system)** Neurodegenerative diseases and dementia disorders (such as Alzheimer's disease, amyotrophic lateral sclerosis and other motor neuron diseases, Creutzfeldt-Jacob's disease and other prion diseases, HIV encephalopathy (AIDS dementia complex), Huntington's disease, frontotemporal dementia, Lewy body dementia and vascular dementia), polyneuropathies (such as Guillain-Barre syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, multifocal motor neuropathy), plexopathies, CNS demyelination (such as multiple sclerosis, acute disseminated/haemorrhagic encephalomyelitis, and subacute sclerosing

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panencephalitis), neuromuscular disorders (such as myasthenia gravis and Lambert-Eaton syndrome), spinal disorders (such as tropical spastic paraparesis, and stiff-man syndrome), paraneoplastic syndromes (such as cerebellar degeneration and encephalomyelitis), CNS trauma, migraine and stroke.

**(other tissues-and systemic disease)** atherosclerosis, acquired Immunodeficiency Syndrome (AIDS), lupus erythematosus; systemic lupus, erythematosus; Hashimoto's thyroiditis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, idiopathic thrombocytopenia purpura; post-operative adhesions, sepsis and ischemic/reperfusion injury in the heart, brain, peripheral limbs hepatitis (alcoholic, steatohepatitis and chronic viral), glomerulonephritis, renal impairment, chronic renal failure and other organs

**(allograft rejection)** acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease.

Furthermore, there is a vast range of causes for the problem and biochemical pathways that mediate all of the diseases or disorders listed on pages 11-15. There is no common mechanism by which all, or even most, of these diseases arise and one treatment cannot be used to treat all the diseases.

For example, Applicants' claims are therefore drawn to a method of treating or preventing Alzheimer's disease. It is the state of the art that there is no known cure or prevention for Alzheimer's disease and that there are only four medications available in

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the United States available to temporarily slow the early stages of Alzheimer's disease. The current drugs for the treatment of Alzheimer disease, Aricept, Exelon, Reminyl and Cognex, treat early stages of Alzheimer's disease by delaying the breakdown of acetylcholine. Memantine, which blocks excess amounts of glutamate treats late stage Alzheimer's disease.

(URL:<http://www.cnn.com/2003/HEALTH/conditions/09/24/alzheimers.drug.ap/index.html>.)

In addition, Layzer, Cecil Textbook of Medicine (article enclosed), states that "some degenerative diseases are difficult to classify because they involve multiple anatomic locations" (see page 2050). Alzheimer's disease has traditionally been very difficult or impossible to prevent or even to treat effectively with chemotherapeutic agents (See e.g., the Cecil Textbook of Medicine, 20<sup>th</sup> edition (1996), Vol. 2, page 1994).

Applicants' claims are also drawn to a method of treating or preventing asthma. Asthma is caused by inflammation in the airways. When an asthma attack occurs, the muscles surrounding the airways become tight and the lining of the air passages swell. This reduces the amount of air that can pass by and can lead to wheezing sounds. Asthma symptoms can be triggered by breathing in allergy-causing substances called allergens or triggers. Triggers include pet dander, dust mites, cockroach allergens, molds pollens. Asthma symptoms can also be triggered by respiratory infections, exercise, cold air, tobacco smoke, etc. Treatment is aimed at avoiding known allergens and respiratory irritants and controlling symptoms and airway inflammation through



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medication. There are two basic kinds of medication for the treatment of asthma. Long-term control medications are used on a regular basis to prevent attacks, not for the treatment during an attack. Types include inhaled steroids, leukotriene inhibitors, Anti-IgE therapy, long-acting bronchodilators, cromolyn sodium or nedocromil sodium, aminophylline or theophylline. Quick relief medications are used to relieve symptoms during an attack. These include: short-acting bronchodilators (inhalers) and corticosteroids. There is no cure for asthma, though symptoms sometimes decrease over time.

Hence, in the absence of a showing of correlation between all the diseases encompassed by the claims as capable of treatment by inhibiting PG2 one of skill in the art is unable to fully predict possible results from the administration of the compound of the claims due to the unpredictability of the role of inhibiting PG2 and, for example, since it is no known cure for Alzheimer's disease and treatment protocols for Alzheimer's disease depend on the stage of the disease.

***The amount of direction present and the presence or absence of working examples***

The only direction or guidance present in the instant specification is the listing of several diseases applicant considers as treatable by the claimed invention found on pages 11-15. There are no working examples present for the treatment of any disease or disorder by inhibiting PG2.

Applicants have disclosed pharmacological data in a ligand binding assay for PGD2 on pages 30-31. Pharmacological activity in general is a very unpredictable

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area. Note that in cases involving physiological activity such as the instant case, “the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.” See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

***The breadth of the claims***

The breadth of the claims is drawn to a method of treating a disease mediated by prostaglandin D2, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt as defined in claim 1. Claim 11 is drawn to a method of treating a respiratory disease in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, as defined in claim 1.

***The quantity of experimentation needed***

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what diseases out of all conditions such as cognitive disorders, hypertension, etc. would be benefited by the inhibition of PG2 would furthermore then have to determine which of the claimed compounds in the instant invention would provide treatment of the diseases.

***The level of the skill in the art***

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be

individually assessed for physiological activity by *in vitro* or *in vivo* screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

The specification fails to provide sufficient support of the broad use of the claimed compounds of the invention in a method of treating a disease mediated by prostaglandin D2. As a result necessitating one of skill to perform an exhaustive search for which diseases can be treated by what compounds of the invention in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that “a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion” and “patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable”.

Therefore, in view of the Wands factors and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

This rejection can be overcome, for example, by deleting the method claims.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11 and 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound of formula (I) or pharmaceutically acceptable salts of said compound does not reasonably provide enablement for a **solvate** of a compound of formula (I). The specification does not provide sufficient guidance nor does it enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In In re Wands, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

In the instant case

***The nature of the invention***

The nature of the invention is a compound of formula I or a pharmaceutically

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acceptable salt thereof. There is no teaching of solvates of the compounds of Formula I in the specification.

***The state of the prior art and predictability or lack thereof in the art***

It is the state of the prior art that the term “solvate” found in the claims is defined as a compound formed by solvation (the combination of solvent molecules with molecules or ions of the solute. It has been estimated that approximately one-third of the pharmaceutically active substances are capable of forming crystalline hydrates. Predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compound (See *Vippagunta, et al.*)

The scope of “solvate” is not adequately enabled or defined. Applicants provide no guidance as how the compounds are made more active *in vivo*. Solvates and hydrates cannot always be predicted and therefore are not capable of being claimed if the applicant cannot properly enable a particular hydrate or solvate.

***The amount of direction or guidance present and the presence or absence of working examples***

There is no direction or guidance present in the specification or working examples present in the specification are that defines or relates to what solvates are being included in the elected invention.

***The breadth of the claims***

The breadth of the claims is a compound of formula I, or pharmaceutically acceptable salt or solvate thereof.

***The quantity of experimentation needed and the level of the skill in the art***

While the level of the skill in the pharmaceutical art is high, the quantity of experimentation needed is undue experimentation. One of skill in the art would need to prepare compounds with various solvents without any direction as to what compounds form solvates with which solvents.

The level of skill in the art is high without showing or guidance as to how to make solvates of a compound of formula (I) it would require undue experimentation to figure out the solvents, temperatures and reaction times that would provide solvates of the above compounds.

To overcome this objection, Applicant should submit an amendment deleting the term "solvates".

**III. Conclusion**

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

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§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shawquia Young whose telephone number is 571-272-9043. The examiner can normally be reached on 7:00 AM-3:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on 571-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Shawquia Young/

Examiner, Art Unit 1626

/Kamal A Saeed, Ph.D./

Primary Examiner, Art Unit 1626